

**II. Rejection of Claims 1-11 under 35 U.S.C. § 112, First Paragraph**

The Examiner has maintained the rejection of claims 1-11. Applicants disagree and respectfully continue to traverse this rejection for at least the following reasons in addition to those already of record.

The Examiner has maintained the rejection of claims 1-11 "because the specification, while being enabling for non-heterocyclic substituted 1,2,9,9a tetrahydro-3H-fluoren-3-ene compounds, does not reasonably provide enablement for compounds containing the HET group." See page 2 of the present Office Action. Applicants respectfully request clarification regarding this statement. The Examiner does not appear to be referring to the claims of the present invention as 1,2,9,9a tetrahydro-3H-fluoren-3-yl compounds are a different class of compounds from those claimed.

**A. *The present application enables one of ordinary skill in the art to make and use the invention commensurate in scope with the present claims.***

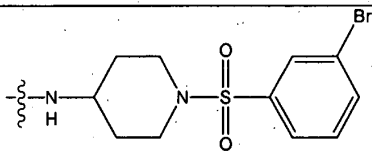
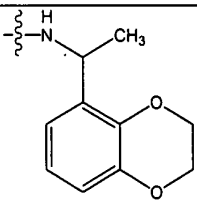
The Examiner asserts that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims." See page 2 of the present Office Action. Specifically, although acknowledging that the present application is enabling for non-heterocyclic substituted compounds, the Examiner asserts that it is not enabling for compounds containing the Het group. *Id.* Because the "Het" groups at R<sup>4</sup>, R<sup>5</sup>, and/or R<sup>10</sup> would be present in compounds of formula IV, the Examiner essentially contends that the specification does not provide guidance for making compounds of formula IV or for linking them to the formula III or formula II/III intermediates. Applicants respectfully disagree.

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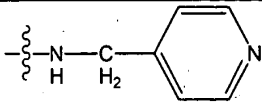
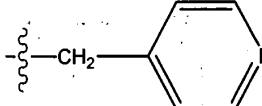
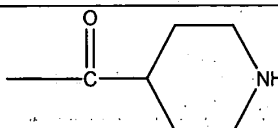
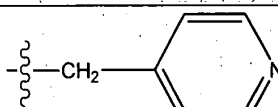
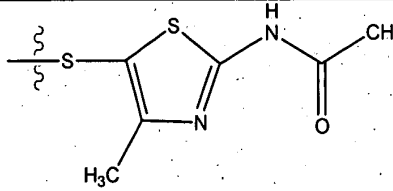
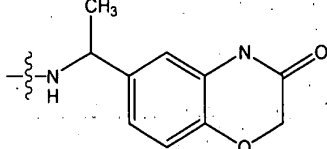
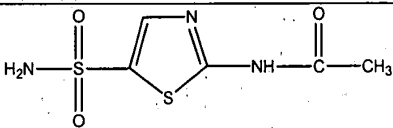
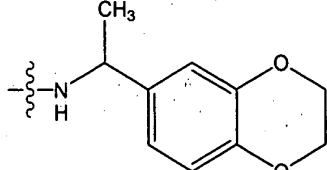
As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. See M.P.E.P. § 2164.01(b). In the present case, the specification discloses at least one method for making and using the claimed invention, including compounds comprising a Het group, that bears the requisite reasonable correlation to the entire scope of the claims.

According to the present application, Het is a residue of a saturated or unsaturated monocyclic or bicyclic, 3-membered to 10-membered heterocyclic ring system containing 1, 2, or 3 identical or different ring heteroatoms chosen from nitrogen, oxygen, and sulfur. See e.g., claim 1; see also paragraphs 22-29. The present specification exemplifies compounds comprising such Het groups. In fact, the present specification contains examples wherein R<sup>4</sup> and R<sup>5</sup> together form a Het group (see e.g., Examples 24, 31, 40, 61, and 68) and examples wherein R<sup>10</sup> is chosen from a Het group (see e.g., Examples 41, 49, 51, 56, and 67). The Het groups in these exemplified compounds are shown below, for the Examiner's convenience.

Example	Het-containing group	Structure of Het-containing group
24	1-(3-bromophenylsulfonyl)piperidin-4-yl	
31	1-(1,4-benzodioxan-5-yl)ethyl	

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Exempl	H t-containing group	Structure of H t-containing group
40	1-(4-pyridyl)methyl	
41	(4-pyridyl)methyl	
49	Piperidin-4-ylcarbonyl	
51	(4-pyridyl)methyl	
56	2-acetylamino-4-methyl-[1,3]thiazole-5-sulfonyl	
61	1-(3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-6-yl)ethyl	
67	1-(4-(morpholin-4-yl)phenyl)ethyl	
68	1-(2,3-dihydrobenzo[1,4]dioxin-6-yl)ethyl	

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Thus, the present specification exemplifies compounds comprising a saturated heterocyclic ring system (Examples 24, 49, and 67), an unsaturated heterocyclic ring system (Examples 40, 41, 51, 56, and 67), both a saturated and unsaturated ring (Examples 31, 61, and 68), a monocyclic heterocyclic ring system (Examples 24, 40, 41, 49, 51, 56, and 67), a bicyclic heterocyclic ring system (Examples 31, 61, and 68), a 5-membered heterocyclic ring system (Example 56), a 6-membered heterocyclic ring system (Examples 24, 40, 41, 49, 51, and 67), a 10-membered heterocyclic ring system (Examples 31, 61, and 68), a heterocyclic ring system containing 1 ring heteroatom (Examples 24, 40, 41, 49, and 51), a heterocyclic ring system containing 2 ring heteroatoms (Examples 31, 56, 61, 67, and 68), a heterocyclic ring system containing nitrogen in the ring (Examples 24, 40, 41, 49, 51, 56, 61, 66, and 67), a heterocyclic ring system containing oxygen in the ring (Examples 31, 67, and 68), and a heterocyclic ring system containing sulfur in the ring (Example 56).

As these exemplified compounds fall within the instant definition of Het groups, Applicants submit that the specification discloses compounds of the claimed invention comprising a Het group which bear a reasonable correlation to the entire scope of the claims drawn to compounds of formula I comprising a Het group.

**1. The specification sufficiently discloses appropriate starting materials for making compounds of formula I comprising a Het group**

In the Office Action, the Examiner asserts that "[t]here is insufficient disclosure of starting materials that would place such a diverse genus of compounds in possession of the public in the event of a patent grant." See page 2 of the present Office Action.

Applicants disagree.

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Applicants submit that, based on the teachings of the specification in general and the Examples in particular, one of ordinary skill in the art may prepare compounds of formula IV comprising a Het group without undue experimentation. For example, according to the specification, compounds of formula IV, as well as formula II and III compounds, "are commercially available or can be readily prepared from commercially available compounds," such as with procedures analogous to those described in the specification or known in the literature. See e.g., paragraph 61 of the specification.

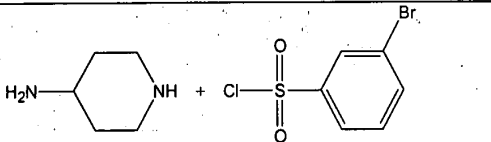
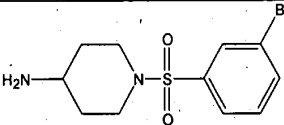
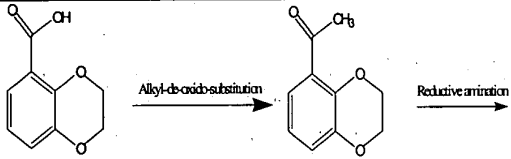
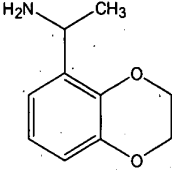
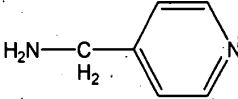
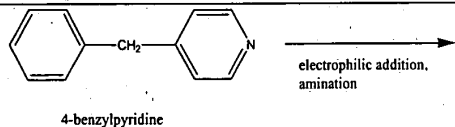
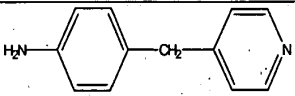
Courts have long recognized that enabled claims may be described with broad language, so long as those of skill in the art can recognize the operable embodiments they comprise without undue experimentation. See e.g., M.P.E.P. § 2164.08(b). In the present case, it would not require undue experimentation for those of ordinary skill in the art to recognize starting materials for compounds of formula IV which are commercially available and may form compounds of formula IV via well known synthetic methods. As previously discussed, organic chemistry textbooks known to those in the art, such as J. March, *Advanced Organic Chemistry*, 4<sup>th</sup> Ed., referred to at paragraph 65 of the specification, provide details and literature sources for a large variety of chemical transformations that may be used to prepare formula IV intermediates. For example, standard methods of aminating heterocycles are well known to those of ordinary skill in the art. See e.g., Exhibits A and B, previously submitted. Moreover, heterocycles themselves may be formed using well known synthetic techniques. See e.g., Exhibit C, previously submitted.

Moreover, as discussed above, the present specification exemplifies ten compounds comprising different Het groups. See Examples 24, 31, 40, 41, 49, 51, 56,

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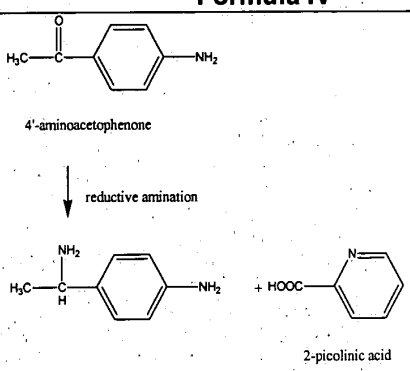
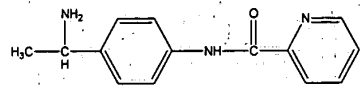
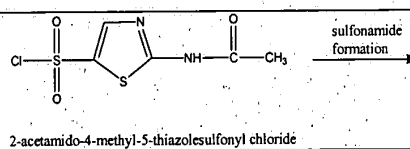
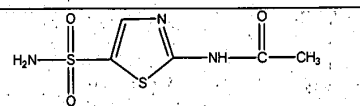
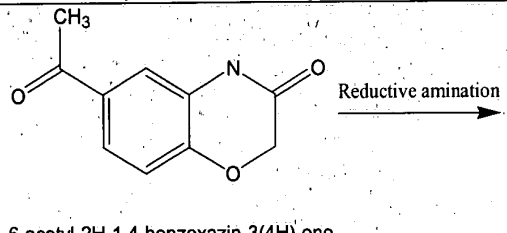
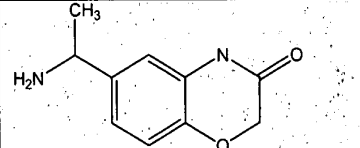
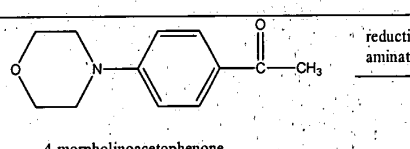
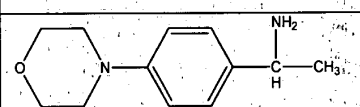
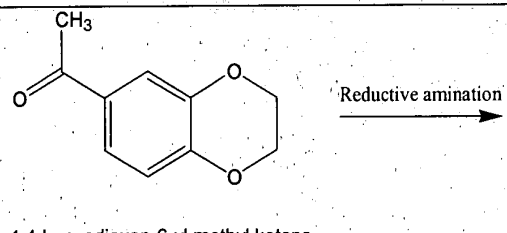
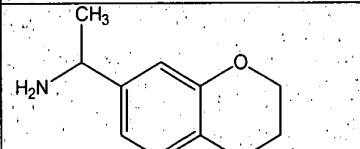
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61, 67, and 68. Compounds of formula IV which would provide the Het groups in these examples are, indeed, commercially available or can be readily prepared from commercially available compounds. Possible compounds of formula IV and their possible syntheses are shown below, for the Examiner's convenience. The starting materials shown below are all commercially available. See Exhibit D, submitted herewith.

Example	Possible Synthesis of Compound of Formula IV	Possible Compound of Formula IV
24	 4-aminopiperidine      3-bromobenzenesulfonyl chloride	
31	 1,4-benzodioxan-5-carboxylic acid    1,4-benzodioxan-5-yl methyl ketone	
40		 4-aminomethylpyridine
41	 4-benzylpyridine	
49	See specification at pages 63 - 65 for detailed synthesis	

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Example	Possible Synthesis of Compound of Formula IV	Possible Compound of Formula IV
51	 <p>4'-aminoacetophenone</p> <p>reductive amination</p> <p>2-picolinic acid</p>	
56	 <p>2-acetamido-4-methyl-5-thiazolesulfonyl chloride</p> <p>sulfonamide formation</p>	
61	 <p>6-acetyl-2H-1,4-benzoxazin-3(4H)-one</p> <p>Reductive amination</p>	
67	 <p>4-morpholinoacetophenone</p> <p>reductive amination</p>	
68	 <p>1,4-benzodioxan-6-yl methyl ketone</p> <p>Reductive amination</p>	

Techniques for synthesizing the potential compounds of formula IV shown above are routine and well known to one of ordinary skill in the art, such as alkyl-de-oxido-substitution using methyl lithium (see Exhibit E) and reductive amination (see Exhibit A, previously submitted, at page 931, top panel of chart, and Example 49, step c, at pages

64-65 of the specification, showing a reductive animation in detail). Further, the knowledge of one of ordinary skill in the art would include potential solvents and protecting groups, if required. Thus, Applicants submit that the specification provides ample guidance for selecting and/or synthesizing appropriate compounds of formula IV comprising a Het group.

Applicants submit that this disclosure alone satisfies the enablement requirement at least because the specification discloses at least one method for making the claimed invention that bears a reasonable correlation to the scope of the claims. See M.P.E.P. § 2164.01(b). A patent application is not meant to be a blueprint for the claimed invention. See M.P.E.P. §§ 2164.01 and 2164.08. Thus, a working example of a particular embodiment is not necessary if one of ordinary skill in the art can make the claimed embodiment without undue experimentation. M.P.E.P. § 2164.02.

Nonetheless, with respect to appropriate starting materials other than those for compounds of formula IV in Examples 24, 31, 40, 41, 49, 51, 56, 61, 67, and 68, Applicants attach herewith pages 73 through 112 of Aldrich Handbook of Fine Chemicals and Laboratory Equipment, 2003-2004, which support Applicants' position that various suitable compounds of formula IV are commercially available. See Exhibit F, submitted herewith.

Accordingly, one of ordinary skill in the art, guided by the specification, the examples, and the knowledge of one of ordinary skill in the art could readily select and/or synthesize compounds of formula IV which are commensurate with the scope of the present claims.

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**2. *The specification enables one of ordinary skill in the art to make compounds of formula I comprising a Het group.***

The instant specification also provides more than adequate support for one of ordinary skill in the art to prepare the claimed compounds, including those comprising a Het group, such as the compounds of Examples 24, 31, 40, 41, 49, 51, 56, 61, 67, and 68. A general procedure for preparing the compounds is provided in the specification beginning at page 34, and is also recited in claim 7. As described in paragraph 58, at pages 34-35, the claimed compounds of the formula I may be formed by linking together three smaller building block compounds of the formulas II, III, and IV. Compounds of the formulas II and III may be reacted together to form an intermediate compound reactive with a compound of formula IV. See specification at paragraphs 62, 63, and 64. Alternatively, formula III and IV compounds may first be reacted together, then linked to a formula II intermediate. *Id.* Paragraphs 65 and 66 of the specification provide further guidance in performing these coupling reactions, by listing potential solvents and protecting groups. Appropriate methods to form the necessary amide linkage between the formula III and IV intermediates would be well known to one of ordinary skill in the art. See e.g., specification at paragraph 64. Further, compounds of the formulas II, III, and IV "are commercially available or can be readily prepared from commercially available compounds by or analogously to procedures described below or in the literature which is readily available to those skilled in the art." See specification at paragraph 61.

Thus, to make compounds of formula I comprising a Het group, one of ordinary skill in the art could readily use the procedures set for in the specification and/or those set forth in Examples 1, 2, 3, 4, 5, 46, 47, 48, and 49. The specification clearly states

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that compounds comprising a Het group can be synthesized analogously to Examples 1-5. See e.g., page 57, paragraph 0100, and page 66, paragraph 0113. Thus, for example, to prepare the compounds of Examples 24, 31, 40, and 61, which comprise a Het group, one of ordinary skill in the art could use the intermediate formed in Example 1(b), i.e., (S)-2-[3(4-cyanophenyl)ureido]propionic acid ethyl ester, and simply react this intermediate with an appropriate compound of formula IV. The cyano group of the compound of formula II could be reduced using the procedure set forth in Example 1(d). For at least this reason, Applicants submit that there is more than adequate guidance in the application for one of ordinary skill in the art to condense appropriate "Het"-containing formula IV compounds with formula III or formula II/III compounds. See also, e.g., paragraphs 64-67.

Thus, for at least the reasons discussed above, Applicants submit that the specification fully enables one of ordinary skill in the art to make the full scope of compounds of formula I as presently claimed, including compounds comprising a Het group.

**B. *The present application enables one of ordinary skill in the art to use the invention commensurate in scope with the present claims.***

In the present Office Action, the Examiner asserts that "there is no reasonable assurance that such an alleged genus of compounds would possess all of the alleged properties for use." See page 2 of the present Office Action. Applicants disagree.

Applicants respectfully point out that claims 1-8 are compound claims.

Applicants have shown that compounds of formula I comprising a Het group display inhibitory properties with respect to factor VIIa. See e.g., Example 73 shows that the

compounds of Examples 40, 61, and 68, which comprise different Het groups and which, do, in fact, possess inhibitory activity with respect to factor VIIa. Accordingly, the present specification discloses at least one method for using the claimed invention that bears the requisite reasonable correlation to the entire scope of the present claims. This disclosure is therefore enabling for compounds comprising a Het group. Only an enabling disclosure is required; Applicants are not required to describe all actual embodiments. See *e.g.*, M.P.E.P. § 2164.02.

Applicants respectfully remind the Examiner that

[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

See M.P.E.P. § 2164.04. As discussed above, the present specification provides ample guidance for making and using the presently claimed compounds of formula I, including compounds comprising a Het group. The Examiner has not set forth any reason to doubt this, nor is there any.

Claims 9 - 12 are the only claims that recite a specific use for the claimed compounds. Claims 9 and 10 recite a method for inhibiting factor VIIa, claim 11 recites a method of inhibiting or reducing blood clotting or inflammatory response, and claim 12 recites a method of treating cardiovascular disorders, thromboembolic diseases, or restenoses. As discussed at page 45 of the specification, inhibition of factor VIIa

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influences blood coagulation and fibrinolysis. Thus, conditions in which a compound of formula I can be favorably used include, *inter alia*, cardiovascular disorders, thromboembolic diseases, and restenosis. See e.g., page 45 of the specification. Applicants do not need to demonstrate that the claimed compounds possess "all of the alleged properties for use" to satisfy method claims 9-12 as asserted by the Examiner, but merely need to display inhibitory properties with respect to factor VIIa which, as described above, has been demonstrated.

Thus, for at least the reasons set forth above, Applicants submit that the specification fully enables one of ordinary skill in the art to make and use the full scope of compounds of formula I as presently claimed, including compounds comprising a Het group. If the Examiner maintains that the claims are not enabled, Applicants respectfully request that the Examiner set forth adequate evidence and reasoning as required by the M.P.E.P. See M.P.E.P. § 2164.04. Otherwise, Applicants request the withdrawal of this rejection, the reconsideration and reexamination of this application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: November 17, 2003

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